REMARKS

Claims 1, 3, 4, 6, 7, 10-13, and 16-43 are pending in this application. Claims 17-37 were previously withdrawn from consideration. Claims 1, 3, 4, 6, 7, 10-13, 16, and 38-43 stand rejected. Claims 1, 12, and 42 have been amended to require that the semiconductor nanoparticle is bound non-covalently to a plurality of cationic polymers. The claim amendments find support on, for example, page 57, lines 19-21 of the specification, as filed. Claim 38 has been amended to correct an inadvertent typographical error. New claims 44-45 have been added and find support, e.g., on page 58, lines 1-7 and Example 16 of the specification, as filed. The amendments add no new matter. Entry of the amendments is respectfully requested.

The amendments to the claims are made solely to obtain expeditious allowance of the instant application and not for reasons related to patentability. Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing or divisional applications hereof containing the canceled, withdrawn, or unamended claims.

Applicants respectfully request reconsideration of the outstanding rejections in view of the following remarks.

Rejections under 35 § USC 103(a)

A. Claims 1, 3, 4, 6, 7, 10-13, 16, 42 and 43 were rejected as allegedly obvious based on Chan et al. (*Science*, 1998, Vol., 281, pp. 2016-2018) in view of Rothbard et al. (US Patent No. 6,495,663).

According to the Office Action, Chan et al. teaches semiconductor quantum dots (nanoparticles), which are biocompatible and suitable for use in cell biology and immunoassays. Chan et al., however, fails to specifically teach a semiconductor nanoparticle complex, wherein the semiconductor nanoparticle is bound to a cationic polymer comprising 5 to 25 continuous lysine (Lys) and/or arginine (Arg) residues. Rothbard et al. was cited to show that drugs and macromolecules can be transported across biological membranes using a conjugate containing a biologically active agent that is covalently attached to a transport polymer (e.g., polymer with 5 to 25 subunits of Lys or Arg).

The combination of references does not establish a *prima facie* case of obviousness for at least the following reasons.

First, the combination of Chan et al. and Rothbard et al. does not teach or suggest all of the limitations in the claims, as amended. Claims 1, 12, and 42 have been amended to require that the semiconductor nanoparticle be bound non-covalently to a plurality of cationic polymers. Chan et al. does not teach or suggest non-covalent attachment of a biomolecule to a semiconductor nanoparticle. Rather, Chan et al. discloses covalent coupling of biomolecules to semiconductor quantum dots. Specifically, Chan et al. teaches a method in which quantum dots are first reacted with mercaptoacetic acid to render the quantum dot water soluble and then coupled covalently to a biomolecule (e.g., using a cross-linking agent such as ethyl-3-(dimethylaminopropyl)carbodiimide (see, Fig. 1 caption).

As mentioned above, Rothbard et al. relates to a conjugate of a biologically active agent and a transport polymer. According to the Office Action, the transport polymer can be a cationic polymer. The conjugate of Rothbard et al. is formed by covalently attaching a biologically active agent to a single transport polymer. Rothbard et al. does not teach or suggest non-covalent attachment of a transport polymer to any type of molecule. In addition, Rothbard et al. does not contemplate conjugates containing more than one transport polymer. Rothbard et al. also does not teach that a transport polymer can be attached to a particle, such as a semiconductor nanoparticle. Thus, even taken in combination, the cited references fail to disclose non-covalent binding of a plurality of cationic polymers to a semiconductor nanoparticle. Accordingly, not all of the elements recited by the instant claims, as amended, are taught by the combination of Chan et al. and Rothbard et al., references.

Second, it continues to be the Applicants' position that the disclosures of the cited references would not have motivated a person of ordinary skill in the art to generate a complex of a semiconductor nanoparticle and a cationic polymer by non-covalent binding the cationic polymer to the nanoparticle. Further, the combination of cited references would not provide the person of ordinary skill with an expectation that the invention as claimed would result in enhanced transport of a semiconductor nanoparticle across a biological membrane.

The Office Action (page 9) states that:

> "Although Rothbard et al.'s method is limited to transporting macromolecules…, one of ordinary skill in the art would have had a reasonable expectation of success in transporting quantum dots of Chan et al. since Chan et al., teaches that quantum dots can be transported across cell membrane in intracellular assays using quantum dots as labels for intracellular labeling (p 2018, Fig. 4)."

The Applicants respectfully disagree with this assertion. As described in detail above, both cited references are directed exclusively to covalent attachment of a biomolecule. The references do not mention or suggest the possibility of non-covalent attachment or recognize any advantage for attaching a biomolecule to a nanoparticle non-covalently. In addition, Chan et al. states that "the mercaptoacetic acid layer is expected to reduce passive protein adsorption on QDs" (page 2017, left hand column), thus implying that non-covalent protein adsorption is undesirable. A person of skill in the art would understand, based on this comment and Chan et al.'s preference for covalent attachment, that non-covalent attachment of a protein to a quantum dot can (and should) be avoided. Rothbard et al., which is also focused solely on covalent attachment of a biomolecule, provides no additional information that would guide a person of skill in the art to seek an alternative to covalent attachment. Thus, in view of the combined teachings in the cited art, such a person would have had no reason to consider attaching cationic polymers to nanoparticles in a non-covalent manner.

A person of ordinary skill in the art would not have been motivated to combine the teachings of Chan et al. and Rothbard et al. for additional reasons, as well. The quantum dots described in Chan et al. include a semiconductor core that is a solid object. This solid object is covered by a coating of many individual molecules of, e.g., mercaptoacetic acid (pg. 2016 and Fig. 1). A protein molecule is attached to each mercaptoacetic acid group to yield the bioconjugate. Rothbard et al. relates to the transport of single molecules across biological membranes and does not disclose or suggest that its carriers would work with particles like a quantum dot. Specifically, Rothbard et al. discloses a conjugate containing a molecule (e.g., a macromolecule or a biologically active agent) that is covalently attached to a single transporter molecule (e.g., a polypeptide). A person of ordinary skill in the art would recognize that the coated quantum dot of Chan et al. has an entirely different structure from the conjugates disclosed by Rothbard et al. The Rothbard et al. conjugates are at least somewhat flexible structures, while the core-shell quantum dot of Chan et al. is a solid object, not able to deform or adapt to its environment. Rothbard et al. does not provide any indication that its peptides are capable of transporting a solid particle across a biological membrane.

Third, even if the Chan et al. quantum dot were coupled to the transport polymers disclosed in Rothbard et al., the resulting complex would produce a quantum dot that would not be expected to result in enhanced transport of the quantum dot across a biological membrane. If, for the sake of argument, one were to couple the transporter molecules of Rothbard et al. with the mercaptoacetic acid groups on the quantum dot disclosed in Chan et al., the result would be a nanoparticle covered in a large number of polycationic groups. Fig. 1 of Chan et al. shows a quantum dot with many

mercaptoacetic acid groups linked to the surface and estimates that for steric reasons only 2-5 molecules of a 100 kD protein can be attached to the nanoparticle. Since polycationic groups having 5-25 Lys or Arg residues would be of significantly lower molecular weight than the proteins identified in Chan et al., it would be likely that many more than 5 of these groups could be attached to the quantum dot.

A nanoparticle with a large number of cationic peptides attached by Chan's method, however, would likely not be suitable for transport into a living cell. Rothbard reports that conjugates containing too many cationic groups inhibit transport across cellular membranes. In particular, Rothbard et al. states that a conjugate with a high-molecular weight polyarginine (12,000 MW) did not cross cellular membranes (col. 12, lines 36-37). The nanoparticle that would result from using polyarginine in Chan's method would produce a nanoparticle covered with many polyarginine molecules (i.e., equivalent to a polyarginine polymer of at least 12,000 MW or more). Such a conjugate having many polycationic groups on a quantum dot could reasonably be expected to act something like the high-molecular weight polyarginine (MW 12,000) from Rothbard: Thus, a person of skill in the art would expect that a quantum dot covered in large amounts of cationic groups (such as polyarginine) on a nanoparticle would not be transported across a biological membrane. With this in mind, the person of ordinary skill would not have combined Chan's nanoparticle with the polycationic groups from Rothbard et al.

Additional information in Rothbard et al. suggests that modifying Chan et al. to use polycationic peptides may produce a complex that will <u>not</u> be useful with viable cells. Rothbard et al. indicates that modifying Chan et al. to use polycationic peptides may create a <u>toxic product</u>. The Office Action (page 10) indicates that the Applicants' argument regarding the toxicity of a nanoparticle having multiple polymers attached to it was not found to be persuasive. The Office Action (page 10) states:

> "Although Chan et al. does not provide method of attaching one polymer peptide to the nanoparticle, Rothbard et al., teaches a method of linking one transport polymer via a suitable linking group (column 7, lines 52-57)."

It is not clear to the Applicants how this comment relates to the arguments set forth by the Applicants in the previously filed paper (e.g., see, pages 22-23). The Applicants respectfully request that the Examiner elaborate on the reasons that the Applicants' previous argument was found not to be persuasive. In addition, the Applicants provide the following further discussion to

aid the Examiner in understanding the distinction between the cited references and the subject matter of the instant claims.

One of the key attributes of Chan et al.'s nanoparticle is its biocompatibility. As discussed above, if the method of Chan et al. were used to attach polycationic peptides to Chan's nanoparticle, the product is likely to be something that resembles the high-molecular weight polyarginine that Rothbard et al. mentions. According to Rothbard et al., "toxicity of the polymers increased with length, though only the 12,000 MW conjugate showed high toxicity at all concentrations tested" (col. 12, lines 41-45). Since the purpose of these conjugates is to transport a molecule or tracer across membranes into a living cell, clearly it would be undesirable to have a toxic moiety as a carrier. Using the method of Chan et al., one would reasonably expect the conjugate to have many polycationic groups and to resemble the longer, more toxic polymers mentioned by Rothbard et al. In view of this, the person of ordinary skill would not have been motivated to employ the methods of Chan et al. to attach polycationic groups from Rothbard et al. to a nanoparticle, because the product would likely be toxic rather than biocompatible, as well as potentially incapable of crossing membranes.

This rejection relies upon the assumption that one of ordinary skill could have simply attached a polycationic group from Rothbard et al. to the quantum dot disclosed in Chan et al., and that such a construct would pass through a biological membrane of a living cell without causing harm to the cell. The only evidence that such a construct would transport through a membrane is Rothbard's data showing that single compounds attached to a single polycationic group attached were able to pass through membranes. A conjugate formed from the nanoparticle of Chan et al. and the cationic polymers disclosed in Rothbard et al. would be covered in numerous cationic groups. Such a complex would have an entirely different structure from the conjugates disclosed in Rothbard et al. and would, therefore, be unlikely to function in a manner identical to the Rothbard et al. conjugates. Given these differences, a person of skill in the art could not have predicted that such a system could be taken up into living cells based on the disclosures of the cited references.

Moreover, Rothbard et al. provides additional reasons for a person of ordinary skill in the art to be dissuaded from affixing a large number of polycationic groups to a nanoparticle for this purpose. Such a construct, which is the logical result of combining Chan's nanoparticles with Rothbard's polycationic groups would be akin to conjugates with 12,000 MW polyarginine that Rothbard showed were both highly toxic and unable to cross membranes. In view of the foregoing, a person of ordinary skill would not have been motivated to combine the teachings of these two references, and would not have had a reasonable expectation that the product made by combining

them would be useful to transport nanoparticles into living cells. The references, therefore, do not support a *prima facie* case for an obviousness rejection. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Claims 38-41 were rejected as allegedly obvious based on Chan et al. (*Science*, 1998, Vol., 281, pp. 2016-2018) in view of Rothbard et al. (US Patent No. 6,495,663) and further in view of Foster et al. (US Patent No. 4,444,879) and Boguslaski et al. (US Patent No. 5,420,016).

This rejection pertains to claims that depend directly or indirectly from claims 1 and 12, and, therefore, include all limitations of claims 1 and 12. Foster et al. and Boguslaski et al. were cited to address added limitations of dependent claims 38-41, but this reference and the reasoning presented in the Office Action do not address the limitations of claims 1 and 12. Therefore, the additional references do not overcome the deficiencies of the combination of Chan et al. and Rothbard et al., discussed in detail above. The dependent claims 38-41 are thus believed to be patentable over the cited references for the same reasons that claims 1 and 12 are patentable over these references. Accordingly, the Applicants respectfully request withdrawal of the outstanding rejection.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (541) 335-0070.

Respectfully submitted,

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/Karen B. Geahigan/
Karen Geahigan, Reg. No. 52,936

Life Technologies
Customer No. 52059
Phone: (541) 335-0070
Facsimile: 541-335-0234